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REVIEW ARTICLE

Colorectal Cancer Screening — Approach, Evidence, and Future Directions

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Introduction

Colorectal cancer is one of the most common cancers worldwide.[1] In the United States, 147,000 individuals received a diagnosis of the disease in 2020, and 53,200 died from it.[2] Most patients with colorectal cancer are older than 50 years of age at diagnosis.[2] Men have a higher risk than do women and are on average 5 to 10 years younger than women when they receive the diagnosis.[3,4]

Most colorectal cancers develop from benign polyps (adenomas and serrated polyps) through a series of genetic and epigenetic changes that take 10 to 15 years.[5–8] Colorectal polyps are very common; about half of individuals 50 years of age and older have polyps.[9,10] Hence, almost all colorectal cancers develop from polyps, but only a small proportion of polyps develop into cancer.[11,12]

Detection and removal of colorectal polyps by colonoscopy hinders progression to colorectal cancer. Because only individuals who get a disease can die from it, the reduction of colorectal cancer incidence by adenoma detection and removal through screening leads to reduced mortality associated with colorectal cancer.[13,14] In addition, screening may detect cancers at an early stage and thereby reduce mortality.

Colorectal cancer development through precursor stages (polyps) over a period of many years and the availability of procedures to detect and remove polyps with little patient harm make colorectal cancer an attractive target for prevention and early detection by population screening.

Screening

Screening means "to sift by passing through a screen."[15] The verb "to sift" derives from an old Dutch word zeef (sieve) for a "utensil used to separate coarser from finer particles of loose material,"[15] which illuminates the main idea behind screening: separating the sick from the healthy.

In contrast to care for symptomatic patients, screening targets presumptively healthy individuals with no clinical signs or symptoms of disease. Because screening targets healthy

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people, it is especially important that its benefits outweigh its harms. A general framework for the benefits, burdens, and harms of screening should be considered before recommending any screening (Table 1).

Cancer screening is usually a process that includes several steps (Fig. 1). Screening involves performing the initial testing, following up with patients with positive results with other tests or procedures to confirm the suspected diagnosis, and treating the diagnosed disease or precursor. Individuals with negative screening results often need to be rescreened at regular intervals to maintain the screening effect, such as yearly or every other year for mammography for breast cancer screening or fecal testing for colorectal cancer screening (Fig. 1). The performance of cancer screening programs includes initial tests and downstream assessment and treatment.[16]

Cancer screening can be divided into two different concepts: preventive screening and early-detection screening (Fig. 2). Both have distinctively different modes of action and different performance abilities. Preventive screening tests aim to detect still-benign cancer precursors. Early-detection screening tests cannot reliably detect benign cancer precursors but aim to detect invasive cancer at an early stage.[17]

PREVENTIVE SCREENING

The identification and removal of benign cancer precursors prevents invasive cancer. Examples of preventive screening tests are colonoscopy and sigmoidoscopy for colorectal cancer screening and the Pap smear for cervical cancer.

The main effect of preventive screening programs is to prevent cancer from developing. Thus, these programs work by reducing cancer incidence. In preventive screening, a reduction in the mortality associated with cancer is mainly a consequence of a reduction in cancer incidence, although most preventive screening tools also provide an opportunity for early cancer detection. Preventive screening can be performed with long time intervals between test rounds, because of the long duration of development from a benign precursor to invasive cancer, which is significantly longer than the growth time from early- to late-stage invasive cancer.

EARLY-DETECTION SCREENING

Most cancers do not have known precursors, or there are currently no tests available to detect them. Thus, preventive screening is not available for most cancers. Breast and prostate cancer screening with mammography and prostate-specific antigen (PSA), respectively, are examples of early-detection screening.

The prerequisite for early detection to reduce mortality is cancer detection at an earlier stage with screening in comparison with no screening. Early detection cannot reduce cancer incidence. In fact, mammography and PSA screening increase cancer incidence by finding small cancers that would not grow further and lead to symptoms or cause death. This is a harm of screening and is called "overdiagnosis."

Colorectal Cancer Screening Tests

A variety of tests are available for colorectal cancer screening. To date, only the guaiac-based fecal occult blood test (gFOBT) and sigmoidoscopy have been shown to reduce the incidence of colorectal cancer and its associated mortality in randomized trials (Table 2). However,

Table 1. A General Framework for the Benefits, Burdens, and Harms of Screening.*

Benefits	Burdens and Harms
Improved prognosis for some patients who have received a diagnosis of disease/disease precursors	Prolonged life with reduced health among some patients in which disease/disease precursor is detected earlier without changing the prognosis
Less invasive treatment for some patients who have received a diagnosis of disease/disease precursors	Overtreatment includes adverse effects of diagnostic procedures and treatment of those with a false-positive screening result, a disease precursor that without treatment would never have developed to disease, or overdiagnosis (disease that would never have caused symptoms or problems during the person's lifetime)
Reassurance for those with a negative screening result	False reassurance for those with a false-negative screening result
	Negative psychosocial effects of false-positive screening results

* This table was adapted from Sørensen et al.[66]

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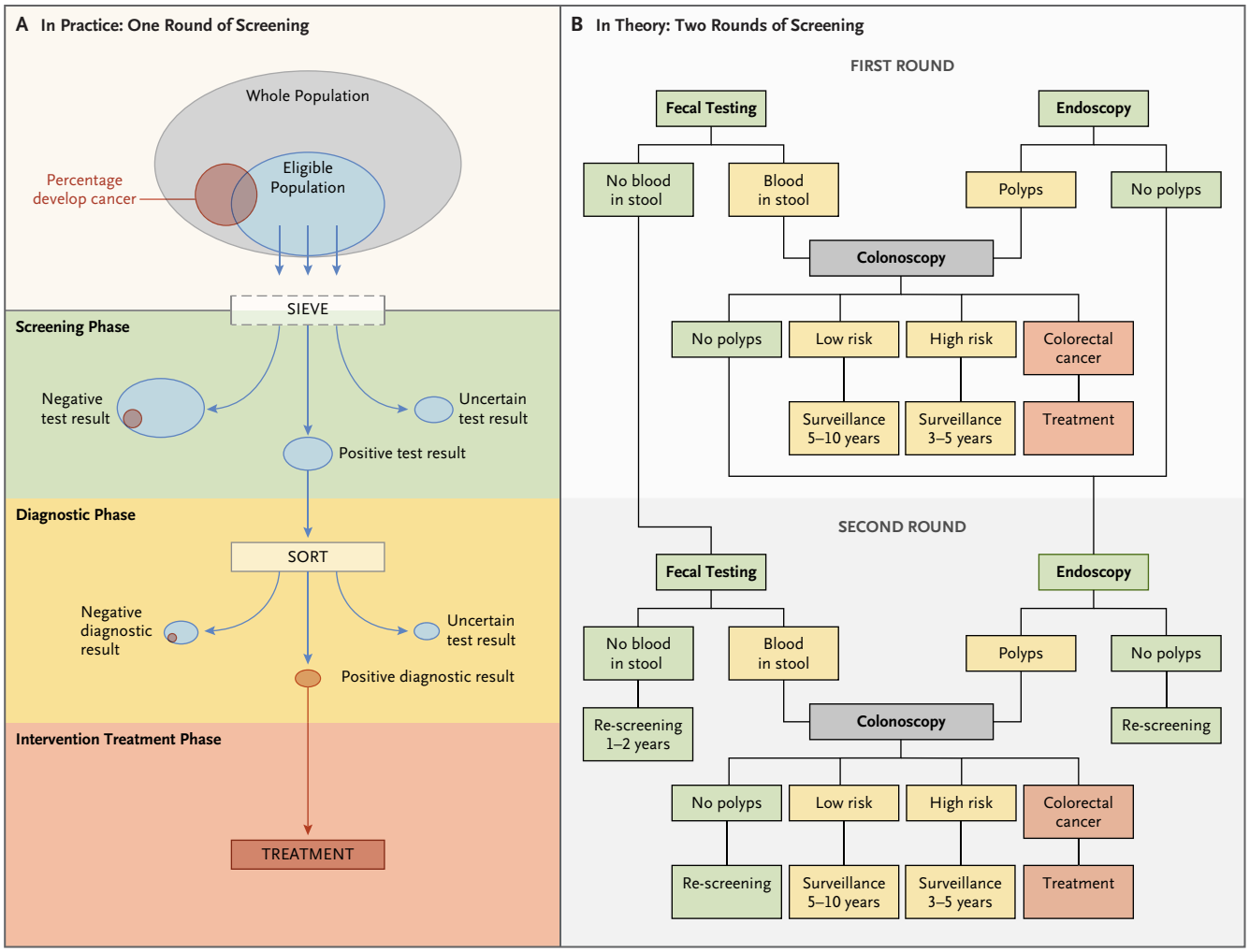

Figure 1. The Colorectal Cancer Screening Process in Practice.

Examples include uncertain test results and false-negative results, and two rounds of colorectal cancer screening with fecal tests and endoscopic tests, without illustrating the uncertain and false test results.

the most commonly applied tests today are the fecal immunochemical test (FIT) and colonoscopy.[18,19]

Large-scale randomized trials are ongoing to compare FIT and colonoscopy or colonoscopy with no screening. Results are expected in 2022.[20] Meanwhile, we rely on results from observational studies and models suggesting that FIT and colonoscopy reduce the incidence of colorectal cancer and its associated mortality.[21] The main concern with observational studies and models is the nonrandom assignment of screening. In brief, the incidence of colorectal cancer and its associated mortality are compared in individuals who have chosen to undergo screening and those who have chosen not to undergo screening. It is well known that attenders and nonattenders usually differ substantially in the risk of cancer and its associated mortality, comorbidities, and socioeconomic status, which causes self-selection bias in nonrandomized screening studies.[22,23] Although the estimates of effectiveness of FIT and colonoscopy on the basis of observational studies and modeling are uncertain, it is reasonable to infer that they should be at least as good as the closely related tests gFOBT and sigmoidoscopy.[21]

Other emerging technologies for colorectal cancer screening — such as computed tomography (CT) colonography, capsule endoscopy, or, most recently, genetic biomarkers

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Screening Type	Incidence	Colorectal Cancer Mortality	Overall Mortality	Overdiagnosis
Preventive Screening (Endoscopy)	Decrease[1]	Decrease[1]	Decrease[3]	Adenomas[4]
Early Detection Screening (Fecal Testing)	Increase[2]	Decrease[2]	No effect[3]	Cancer[4]
Preventive Screening (Positive Fecal Tests)	Dependent on the number of people who undergo endoscopy	Decrease[1,2]		Adenomas[4] Cancer[4]

——— Observed (certain) outcomes - - - - - Expected (uncertain) outcomes

1 Increased detection of premalignant adenomas may contribute to cancer prevention and reduce colorectal cancer mortality.

2 More cancers will be diagnosed at earlier stage, while overall detection rate of invasive cancer may be higher. This may lead to an increase in colorectal cancer incidence and a reduction in colorectal cancer mortality.

3 Only sigmoidoscopy screening has shown a potential reduction in overall mortality in randomized controlled trials.

4 Overdiagnosis of adenomas and cancer may result in higher costs, burdens and harms related to treatment and surveillance of detected lesions.

Figure 2. Main Characteristics of and Tools for Preventive and Early-Detection Screening.

in feces or blood — may play a role in future screening, but most are not used commonly worldwide.

FECAL SCREENING

Fecal testing is a stepwise screening strategy that needs to be repeated at regular intervals. All positive fecal tests need to be followed by colonoscopy to confirm the diagnosis and remove detected polyps (Fig. 1).

Fecal occult blood testing is primarily an early-detection screening test. The theory is that early colorectal cancers bleed and that small traces of blood can be detected in the stool before symptoms develop. Since many cancers bleed intermittently, the sensitivity of a fecal test is limited. Thus, fecal testing needs to be repeated. The optimal interval between fecal screening rounds and the number of tests in each round, as well as the age of screening start and end, are debated.[24] Most current guidelines recommend repeating fecal testing yearly or every other year.[18,19,25]

There are several reasons why fecal tests may be positive, such as bleeding polyps, inflammation, peptic ulcers, or hemorrhoids. Although fecal testing works primarily through the early detection of cancer, it may also prevent some cancers, owing to the coincidental finding and removal of polyps in people undergoing colonoscopy because of a positive fecal test.

Previously, fecal testing was performed with gFOBT, but this test has been replaced with the FIT, providing more specific detection of colorectal disease (because there are no false-positive results from dietary sources and upper gastrointestinal causes of bleeding such as peptic ulcer disease) and allowing quantitative measurement of the amount of hemoglobin in feces (in micrograms of hemoglobin per gram of feces).[26,27] FITs can be adjusted for the desired threshold of fecal hemoglobin for a positive test, thus allowing adjustment of the sensitivity and specificity of colorectal cancers and adenomas in screening programs.[28]

Different FIT screening programs apply different cutoffs depending on the priorities of benefits, harms, capacity, and costs. For example, the colorectal cancer screening program in England uses a FIT positivity threshold of 20 μg Hb/g, whereas the Scottish program applies a positivity threshold of 80 μg Hb/g.[29] It is unknown whether screening benefits and harms in the incidence of colorectal cancer and its associated mortality differ between programs with different thresholds.[28,30,31]

ENDOSCOPIC SCREENING

Endoscopic screening may be performed with sigmoidoscopy (examining the distal part of the colon) or colonoscopy (examining the whole colon). Colonoscopy is currently the predominant endoscopic screening test.

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Table 2. Screening Effect on the Incidence of Colorectal Cancer and its Associated Mortality.*

CRC Outcomes	Study Results and Measurements (95% CI)	Anticipated Absolute Effects (per 1000)†		Certainty of the Evidence (GRADE)
		With No Screening‡	Risk Difference with Screening (95% CI)	
Sigmoidoscopy versus no screening				
Incidence	0.78 (0.74 to 0.83)§	26	6 fewer (7 to 4 fewer)	High
Mortality	0.74 (0.68 to 0.80)§	9	2 fewer (3 to 2 fewer)	High
Incidence distal colon	0.67 (0.60 to 0.75)§	26	9 fewer (10 to 7 fewer)	High
Mortality distal colon	0.61 (0.49-0.74)§	9	4 fewer (5 to 2 fewer)	High
Biennial gFOBT versus no screening				
Incidence	0.85 (0.74 to 0.96) to 1.02 (0.93 to 1.12)¶	26	4 fewer (7 to 1 fewer) to 1 more (2 to 3 more)	High
Mortality	0.78 (0.65 to 0.93) to 0.91 (0.84 to 0.98)¶	9	2 fewer (3 to 1 fewer) to 1 fewer (1 to 0 fewer)	High
Annual gFOBT versus no screening				
Incidence	0.81 (0.71 to 0.93)‖	26	5 fewer (8 to 2 fewer)	Moderate (because of serious imprecision)
Mortality	0.68 (0.56 to 0.82)**	9	3 fewer (4 to 2 fewer)	High

* These estimates are taken from the 2021 U.S. Preventive Services Taskforce Evidence Review[26] unless otherwise specified. CI denotes confidence interval, CRC colorectal cancer, gFOBT guaiac-based fecal occult blood test, GRADE Grading of Recommendations Assessment, Development and Evaluation, IRR incidence rate ratio, and RR relative risk.

† The risk in the screening group is based on the assumed risk in the no-screening group and the relative effect of the screening intervention (and its 95% CI).

‡ The risk with no screening is meant as an illustration and is based on estimates of cumulative risk of colorectal cancer and colorectal cancer death from 45 to 80 years of age from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) Explorer Application (https://seer.cancer.gov).

§ IRRs based on data from 458,002 individuals from four randomized trials (follow-up: 11 to 17 years; attendance: 58 to 84%).

¶ RRs based on data from 419,966 individuals from five randomized trials (follow-up: 11 to 30 years; screening rounds: 2 to 9; attendance: 60 to 90%).

‖ RRs based on data from 30,913 individuals from one randomized trial (follow-up: 18 years; screening rounds: 11; attendance: 90%).

** RRs based on data from 30,964 individuals from one randomized trial (follow-up: 30 years; screening rounds: 11; attendance: 90%).

Endoscopic screening aims to detect and remove adenomas and serrated polyps, and thus prevent colorectal cancer. In addition, cancers may be detected early at endoscopic screening. The expected reduction in mortality associated with colorectal cancer is mainly attributable to the reduction of cancer incidence by the removal of polyps and, to a lesser degree, to early detection and treatment of early cancer.[32]

Sigmoidoscopy is a less invasive procedure than colonoscopy and can be performed without sedation, with bowel preparation limited to an enema. Colonoscopy requires more cumbersome oral bowel preparation, is more time consuming, and is most often performed with conscious sedation or general anesthesia.[33] In addition to being used as a primary screening test, colonoscopy is the common follow-up procedure for individuals who have a positive test result on any other colorectal cancer screening test (Fig. 1).

EMERGING SCREENING TESTS

One fecal biomarker panel test is currently recommended by some U.S. guidelines but not in other parts of the world, owing to the high costs and limited evidence of benefits in the incidence of colorectal cancer and its associated mortality.[26,34]

Many commercial entities and academic institutions are currently investigating novel blood-based screening tests using genetic, epigenetic, or proteomic markers for colorectal cancer or polyps, but no test is currently at the approval stage for use in screening programs.

CT colonography is recommended as a second-tier screening test in some U.S. guidelines. However, because of its high costs, radiation exposure, and need for follow-up colonoscopy of all CT positive results, CT colonography is not currently used in population screening.

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Postscreening Surveillance

Patients who had polyps removed at screening are classified as having a high or low risk for future development of colorectal cancer, dependent on the size, number, and histologic features of the removed polyps. Most individuals with removed polyps receive surveillance colonoscopy — for example, every 3, 5, or 10 years, depending on the polyp characteristics (Fig. 1). Guidelines for surveillance after polyp removal vary in different parts of the world, with more surveillance and shorter intervals in the United States and less surveillance for fewer people in Europe.[35–37]

There is a lack of high-quality studies guiding recommendations for surveillance after colorectal cancer screening. Thus, all current recommendations are based on low-quality evidence using surrogate end points such as recurrent adenomas and expert opinion. Currently, a 20,000-patient European randomized trial comparing different polyp surveillance strategies for patients with removed polyps is ongoing, and a U.S. National Institutes of Health–sponsored sister trial is about to begin.[38,39]

Benefits and Harms

Table 2 shows the relative and absolute benefits of sigmoidoscopy and gFOBT, the colorectal cancer screening strategies that have been tested in randomized trials. The certainty of the evidence is high, because we have included randomized trials only — with the exception of colorectal cancer incidence with yearly gFOBT, where we have graded the certainty as moderate owing to imprecision in the effect estimate. For colonoscopy and FIT, the results from randomized trials are not yet available. We assume a relative effect of colonoscopy and FIT similar to that observed in the randomized trials of sigmoidoscopy and gFOBT. Because sigmoidoscopy does not reach the full colon, we have assumed the effect of colonoscopy to be similar to the effect of sigmoidoscopy in the distal colon (Table 2).

As shown, the benefits and harms of screening depend on the screening test, with a larger effect of colonoscopy (Fig. 2; Tables 2 and 3) compared with sigmoidoscopy and FIT/gFOBT. However, the magnitude of effect is more dependent on the individual risk of cancer than on which tests are used. Screening individuals with a 2% risk of colorectal cancer may prevent 0 to 7 cancers and hinder 1 to 3 deaths from colorectal cancer per 1000 individuals screened (Fig. 2). Screening individuals with a 4% risk of colorectal cancer may prevent 1 to 13 cancers and hinder 2 to 7 colorectal cancer deaths per 1000 individuals screened.

All tests have some adverse effects; bleeding and perforations are the most common adverse events for endoscopy (Table 3). The number of adverse events is dependent on the number of endoscopies, performed either as a primary screening test, as a follow-up to a positive sigmoidoscopy or fecal test, or for surveillance (Fig. 1). In FIT screening programs, the number of adverse events increases with a lower cutoff for FIT positivity.[40] The number of adverse events also increases with increased age, the number of comorbidities, and in colonoscopies with polypectomies.[41]

There is considerable heterogeneity in the reports on screening-related harms; the indications for colonoscopy differ, there is no standard nomenclature for all harms, sources of information vary, and often it is unclear how adverse events are captured.[14,42] Mostly, harms related to surveillance colonoscopies are not included in the harm of screening in population-based studies, so the present estimates of burdens and harms are highly uncertain.[25,43]

OVERDIAGNOSIS

Overdiagnosis in cancer screening is defined as the detection of a lesion (e.g., a polyp or cancer) that would not have caused symptoms or death (or polyps that would not have progressed to cancer) in the remaining lifetime of the individual who received the diagnosis. Of note, overdiagnosis is not the same as a false-positive test result.

Overdiagnosis is inherently associated with patient harm. However, it is not possible to disentangle whether an individual patient has received an overdiagnosis, because overdiagnosed disease cannot be distinguished from nonoverdiagnosed disease with the currently available screening tests. The risk of overdiagnosis with screening must be estimated on a population level. The precise risk of overdiagnosis with colorectal cancer screening is currently unknown[44,45] but is believed to be smaller than for prostate cancer screening.

Overdiagnosis is harmful because it leads to unnecessary treatment, labels individuals as diseased who would not have negative consequences if they had not been screened, causes psychosocial harm such as anxiety, and

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Table 3. Serious Bleeds and Bowel Perforations per 1000 Endoscopies.*

Outcomes	Study Results and Measurements	Anticipated Absolute Effects (per 1000)†		
		With No Screening‡	Risk Difference with Screening (95% CI)	Certainty of the Evidence (GRADE)
Sigmoidoscopy screening				
Serious bleeds	Based on data from 179,854 individuals from 10 studies	0	0 more (0 to 0)	Moderate (because of risk of bias)
	Follow-up: 30 d or not specified			
Perforations	Based on data from 359,679 individuals from 11 studies	0	0 more (0 to 0)	Moderate (because of risk of bias)
	Follow-up: 30 d or not specified			
Colonoscopy performed after abnormal sigmoidoscopy				
Serious bleeds	Based on data from 5790 individuals from four studies	0	2 more (1 to 3 more)	Moderate (because of risk of bias)
	Follow-up: 30 d or not specified			
Perforations	Based on data from 23,022 individuals from four studies	0	1 more (1 to 2 more)	Moderate (because of risk of bias)
	Follow-up: 30 d or not specified			
Colonoscopy performed after abnormal gFOBT or FIT				
Serious bleeds	Based on data from 78,793 individuals from 11 studies	0	2 more (1 to 3 more)	Low (because of risk of bias and indirectness)
	Follow-up: 30 d or not specified			
Perforations	Based on data from 341,922 individuals from 12 studies	0	1 more (0 to 1 more)	Low (because of risk of bias and indirectness)
	Follow-up: 30 d or not specified			
Colonoscopy screening				
Serious bleeds	Based on data from 5.4 million individuals from 22 studies	0	2 more (1 to 2 more)	Moderate (because of risk of bias)
	Follow-up: 7 to 30 d or not specified			
Perforations	Based on data from 5.4 million individuals from 23 studies	0	0 more (0 to 0)	Moderate (because of risk of bias)
	Follow-up: 7 to 30 d or not specified			
Colonoscopy with polypectomy				
Serious bleeds[41]	Risk of event in a cohort undergoing colonoscopy with polypectomy compared with a matched cohort without colonoscopy Based on data from 29,988 procedures from one study	2	7 more	Moderate (because of indirectness)
	Age group: 66 to 95 yr			
	Follow-up: 30 d			
Perforations[41]	Risk of event in a cohort undergoing colonoscopy with polypectomy compared with a matched cohort without colonoscopy	0	1 more	Moderate (because of indirectness)
	Based on data from 29,988 procedures from one study			
	Age group: 66 to 95 yr			
	Follow-up: 30 d			

* These estimates are taken from the 2021 U.S. Preventive Services Taskforce evidence review[26] unless otherwise specified. CI denotes confidence interval, FIT fecal immunochemical test, GRADE Grading of Recommendations Assessment, Development and Evaluation, and gFOBT guaiac fecal occult blood.

† The risk in the screening group is based on the assumed risk in the no-screening group and the relative effect of the screening intervention (and its 95% CI).

‡ For serious bleeds and perforations, we assumed a risk of 0 per 1000 with no screening (studies do not report the risk in comparison groups without screening). However, for the outcome colonoscopy with polypectomy, the estimates are based on a matched cohort study and hence include the baseline risk in the matched cohort.

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has economic consequences related to health care costs or insurance premiums.[46–48] Furthermore, screening may lead to unnecessary medical consequences, such as surveillance and follow-up, with the risk of more overdiagnosis and exposure to harms.

Both preventive and early-detection colorectal cancer screening entail different risks of overdiagnosis. Overdiagnosis of colorectal cancer is more severe than overdiagnosis of polyps, because cancer treatment is more excessive and harmful than polyp treatment. However, because there are many more patients with polyps than with cancer, the harm of population screening even for polyp overdiagnosis in preventive screening deserves consideration by policymakers and screening providers. The prevalence of adenomas in an average screening population of individuals 60 years of age was 32%[49] and the lifetime risk of colorectal cancer in the United States is about 4.2%.[50] Consequently, most adenomas will not progress to cancer.

QUALITY VERSUS OVERDIAGNOSIS

The success of preventive screening tests for colorectal cancer relies on their reliable detection of premalignant polyps. During the past 10 years, there has been increasing recognition of a large variation in the endoscopist's ability to adequately detect and remove polyps.[10,51,52] Individuals who have their colonoscopy performed by an endoscopist with high adenoma detection rates (ADRs) have a significantly lower risk for colorectal cancer than those examined by an endoscopist with low detection rates. Consequently, rigorous quality assurance programs including training, supervision, and auditing have been introduced in many colorectal cancer screening programs.

However, the exact relationship between ADRs and future cancer prevention is still unknown. Some propose a linear relationship,[10] whereas others have suggested a threshold effect; for example, an additional ADR increase over a specific threshold such as 20% ADR may have little or no benefit in cancer prevention but may increase polyp overdiagnosis and overtreatment.[52] If there is a threshold between ADR and colorectal cancer prevention, the risk of causing harm to patients as a result of unnecessary polyp removal will increase with increasing the ADR above the threshold, and it will result in additional cost and burden for patients and health systems without significant additional benefit.[44,53]

Artificial intelligence (AI)–based polyp detection tools during colonoscopy have recently been introduced to increase polyp detection. Preliminary studies suggest that AI-based polyp detection aids during colonoscopy increase the average ADR of endoscopists from 25 to 37%.[54] The AI aids did not increase the detection of larger and advanced polyps, those with the highest risk for malignant transformation[55]; in addition, it is unknown whether AI benefits for small polyp detection lead to better cancer prevention in colorectal cancer screening.

Although there is benefit of increased ADR to an unknown threshold, AI aids and other measures to increase ADR will inevitably increase the screening burden as a result of the intensive surveillance recommended for more patients.

Guidelines

Clinical practice guidelines have become important tools to facilitate evidence-based clinical practice, but they may also have negative effects and pose ethical challenges (Table 4). Many national and international clinical practice guidelines exist for colorectal cancer screening. Most recommend screening for average-risk individuals between 50 and 79 years of age.[18,19] Recently, some U.S. guidelines such as those from the U.S. Preventive Services Task Force[25] and the American Cancer Society[56] have changed the recommended starting age for screening to 45 years.

Because of the lack of data from randomized controlled trials for commonly applied colorectal cancer screening tests such as FIT and colonoscopy, several guidelines base their recommendations on estimates of benefits and harms of screening from microsimulation modeling.[25,43,56] Models rely on several assumptions, including the unknown natural history of colorectal cancer, and the validity of the modeled outputs is uncertain.[57,58] It is important to acknowledge the uncertainty when recommendations are based on modeling.[43]

Screening leads to a large clinical benefit for some, but it exposes many to burden and potential harm. Colorectal cancer screening is not a one-time event; rather, it results in follow-up colonoscopy and surveillance for many individuals (Fig. 1). People may value the potential benefits and harms differently, and some may reasonably decline screening.[43,59] There is currently no established threshold of what magnitude of benefit people would want to undergo screening, given its harms and burdens.

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Table 4. Examples of Ethical Challenges with Clinical Practice Guidelines	
Challenge	**Example**
Not individually applicable	Peoples' values and preferences differ; hence, guidance based on evidence from populations may not be applicable to the individual.
Opposing and biased recommendations	Different guidelines may give completely different recommendations in equal or similar situations as a result of different guideline development methods, different interpretations of the available evidence, and different interests among the guideline developers.[67]
Interpreted as rules	Guidelines, especially strong recommendations, may be interpreted as the "only one right action" in a given situation,[68] and legal litigation is, in some instances, experienced by clinicians who have not followed guideline recommendations.
Reduces quality of care	Guideline recommendations may cover a clinician's back but may also reduce the sense of personal responsibility and leave less space for nuances and individualization of clinical practice, which may have a negative effect on the quality of care.[68]
Hinders research	Too much emphasis on guideline recommendations may also affect new knowledge generation when research that is not in accordance with guideline recommendations is (misguidedly) regarded as unethical, even if the underlying evidence for the recommendations is very weak or lacking.[69]

Most previous colorectal cancer screening programs recommend screening to everyone older than a certain age and do not consider individual cancer risk. A more recent colorectal screening guideline proposes the introduction of risk and benefit thresholds for recommending for or against screening.[43] The proposed threshold is based on the balance of absolute benefits and harms and used an expert and patient panel to provide guidance on what most people would choose.[60] On the basis of such a benefit threshold, the panel recommended screening (weak recommendation) for individuals with a 15-year risk of colorectal cancer of 3% or higher and no screening when it is below 3% (Fig. 3). Calculators have been developed for individuals to ascertain their personal risk.[43]

Access and Informed Choice

Although there are several screening tests and recommendations, colorectal screening is not accessible to all. Insurance coverage is essential to secure equal access to preventive services, reducing disparity. Limited evidence is available to understand other contributors to disparity, and no clear evidence exists for effective interventions to overcome them.[61] Patient navigation (telephone interviews, reminders, patient navigators) may increase participation in screening for colorectal cancer.[61] However, the magnitude of the increase varies, and whether it is accompanied by a reduction in the mortality associated with cancer is uncertain. Furthermore, participation may be a suboptimal measure of disparity in preventive services. Too strong a focus on participation may hinder individual informed choice and shared decision-making.[62,63]

Many guidelines weigh benefits versus harms when developing recommendations, but few quantify net benefits.[60] Information such as the absolute risk for colorectal cancer, the absolute benefit of the screening test to reduce that risk, and the absolute risk for harms from the full screening process must be included for individuals to make an informed choice.

The Future: Learning Screening Programs

New screening interventions, whether new tests or changing the number of tests or test intervals, screening starting and stopping ages, or cutoffs for test positivity, should ideally be tested in clinical trials. However, when screening is widespread and the population is exposed, traditional clinical trials are not possible because there is no valid control group for comparison of screening benefits and harms.

A novel approach to reliably quantify the benefits and harms of preventive services, in the absence of randomized controlled trials, is the establishment of learning health systems. Learning health systems utilize randomized implementation and deimplementation studies and have been described in detail elsewhere.[64,65] A learning screening program for colorectal cancer screening, which continuously and systematically generates knowledge about which test is most effective to reduce mortality, offers the optimal balance between benefits and harms; this is most likely to be acceptable in the population and thus could be established immediately.[65]

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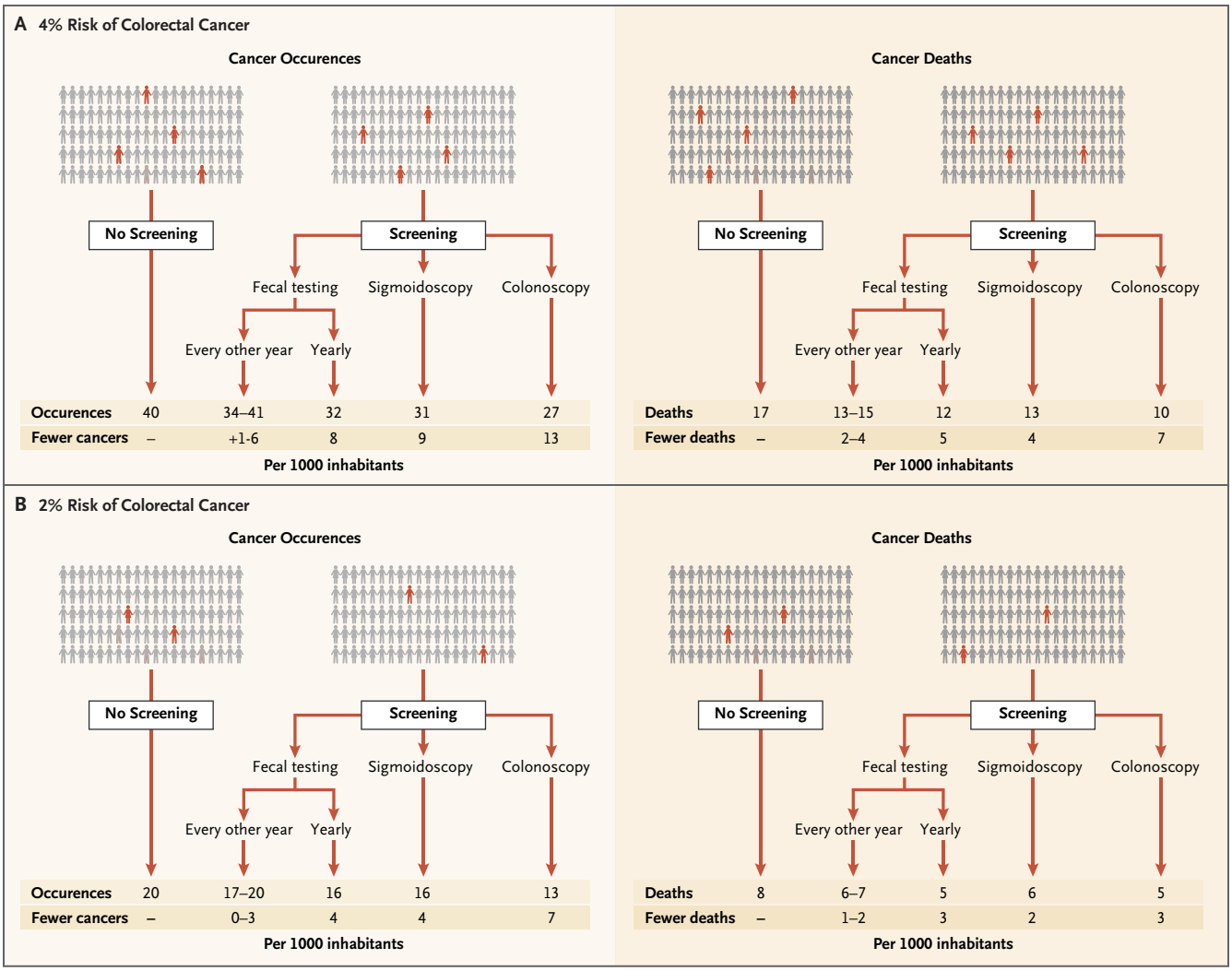

Figure 3. Benefits of Screening with Different Tests.

Summary

Colorectal cancer screening works through the early detection and/or prevention of cancers and is a process with several tests. There are currently no randomized trials of FIT and colonoscopy (the most widely used tests), but these are likely to perform at least as well as gFOBT and sigmoidoscopy, which have been shown in randomized trials to reduce the incidence of colorectal cancer and its associated mortality.

The potential absolute benefits of screening vary with the individual cancer risk, whereas harms from screening depend largely on the number of colonoscopies performed in the screening process. Estimates of both benefits and harms from the full screening process are uncertain, and guidelines should acknowledge that people may value potential benefits and harms from screening differently. When screening is widespread, new and more efficient testing strategies, including those addressing screening frequency and age range, should be tested systematically and continuously in learning screening programs.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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